

We claim:

1. A method for treating an insulin responsive disorder in a mammal comprising:
  - (a) introducing nucleic acid encoding a variant proinsulin into a host cell having a constitutive pathway of protein secretion to generate an engineered host cell, said variant proinsulin having a non-naturally occurring cleavage site, the cleavage site being recognizable by a host cell processing enzyme, and said engineered host cell being capable of producing insulin in response to glucose; and
  - (b) administering a therapeutically effective amount of said engineered host cell to said mammal.
2. The method of claim 1 wherein said nucleic acid further encodes a glucose transporter protein and glucokinase.
3. The method of claim 1 wherein said nucleic acid further encodes a glucose response element.
4. The method of claim 1 wherein said nucleic acid is introduced into said host cell by infection with a virus.
5. The method of claim 1 wherein said host cell is a muscle myoblast cell.
6. The method of claim 1 wherein said engineered host cell is administered in a pharmaceutically acceptable carrier.
7. The method of claim 6 wherein said engineered host cell is introduced intraperitoneally or subcutaneously into said mammal.

8. The method of claim 1 wherein said non-naturally occurring cleavage site is a prohormone convertase site.
9. The method of claim 8 wherein said prohormone convertase site is ZXZR, wherein Z is LYS or ARG; X is any amino acid; and R is ARG.
10. The method of claim 1 wherein said non-naturally occurring cleavage site is at a location selected from the group consisting of the proinsulin B-/C-chain junction, the A-/C-chain junction, and the B-/C-chain junction and the A-/C-chain junction.
11. The method of claim 1 wherein said variant proinsulin further comprises aspartic acid at B chain residue 10.
12. The method of claim 1 wherein said introduced nucleic acid further comprises nucleic acid encoding said host cell processing enzyme.
13. The method of claim 12 wherein said host cell processing enzyme is furin.
14. The method of claim 1 wherein said mammal has or is at risk of developing diabetes.
15. The method of claim 2 wherein the glucose transport gene is GLUT-2.
16. A method for treating an insulin responsive disorder in a mammal comprising:
- (a) introducing nucleic acid encoding a variant proinsulin into a plasmid to generate a proinsulin-producing plasmid, said variant proinsulin having a non-naturally occurring cleavage site, the cleavage site being recognizable by a processing enzyme of a mammalian

host cell having a constitutive protein secretion pathway; and

(b) administering a therapeutically effective amount of said proinsulin producing plasmid to said mammal.

17. The method of claim 16 wherein said plasmid is administered as a liposome.
18. The method of claim 16 wherein said proinsulin is produced by said mammal and cleaved by said processing enzyme of said mammalian host cell to produce insulin in response to glucose.
19. The method of claim 16 further comprising nucleic acid encoding a glucose response element.
20. The method of claim 16 wherein said nucleic acid encoding said variant proinsulin is methylated.
21. An engineered host cell comprising nucleic acid encoding a glucose response element and nucleic acid encoding a variant proinsulin, the variant proinsulin having a non-naturally occurring cleavage site, said cleavage site being recognizable by an engineered host cell processing enzyme.
22. The engineered host cell of claim 21 wherein said engineered host cell processing enzyme is furin.
23. The engineered host cell of claim 21 wherein said nucleic acid further comprises nucleic acid encoding a glucose transporter protein and glucokinase.

24. The engineered host cell of claim 21 wherein said engineered host cell processing enzyme is not naturally occurring in said engineered host cell.
25. The engineered host cell of claim 24 having nucleic acid encoding an engineered host cell processing enzyme not naturally occurring in said engineered host cell.
26. The engineered host cell of claim 21 wherein said host cell is a muscle myoblast cell.
27. The engineered host cell of claim 21 wherein said nucleic acid encoding said variant proinsulin is methylated.
28. A method for preparing a host cell capable of producing insulin from variant proinsulin comprising introducing into a host cell not naturally capable of forming secretory granules nucleic acid encoding a variant proinsulin having a non-naturally occurring cleavage site, said cleavage site being recognizable by a host cell processing enzyme.
29. A method for treating a mammalian patient comprising:
- (a) obtaining a host cell having a constitutive pathway of protein secretion,
  - (b) introducing nucleic acid encoding a desired polypeptide into the host cell to generate an engineered host cell, and wherein the desired polypeptide has a non-naturally occurring cleavage site, the cleavage site being recognized by an engineered host cell processing enzyme, and
  - (c) administering a therapeutically effective amount of said engineered host cell to said mammal.

30. The method of claim 29 further comprising introducing into said engineered host cell nucleic acid encoding a variant proinsulin capable of being processing to insulin by said engineered host cell.
31. The method of claim 33 further comprising introducing into said engineered host cell nucleic acid encoding a GLUT protein and glucokinase.